Intravenous Ethanol Infusions Can Mimic the Time Course of Breath Alcohol Concentrations Following Oral Alcohol Administration in Healthy Volunteers

Vijay A. Ramchandani, Martin Plawecki, Ting-Kai Li, and Sean O'Connor

Background: Our previous studies have used intravenous (IV) clamping methods to demonstrate that family history positive (FHP) subjects exhibit a greater initial response to alcohol than family history negative (FHN) subjects. These results differ from other studies of family history of alcoholism (FHA) influences, most of which have used an oral alcohol challenge, suggesting that the route of administration may influence both the response to alcohol and FHA-related differences in response. To examine this possibility, one approach would be to directly compare responses following oral and IV alcohol administration in the same subjects. There is, however, a 3- to 4-fold variance, between- and within-subjects, in the breath alcohol concentrations (BrACs) following oral alcohol administration. Thus, our objective was to characterize the between-subject variability in the time course of BrACs following oral alcohol administration in healthy volunteers and to develop an IV infusion method to mimic the BrAC-time course attained following oral alcohol in the same subject.

Methods: This was a 2-session study in young adult, healthy, nondependent drinkers. In the first session, subjects ingested an oral dose of alcohol, based on total body water, to achieve a target peak BrAC of 80 mg%. In the second session, subjects received an IV infusion of ethanol designed to achieve the same BrAC time course as that achieved in the first session. The individualized infusion-rate profile was precomputed using a physiologically-based pharmacokinetic (PBPK) model for alcohol with model parameters adjusted to the individual's physiology. The peak BrACs (C_{max}), times of peak BrAC (T_{max}), and the areas under the BrAC vs. time curve (AUC) were compared between sessions to assess how closely the BrAC exposure during the IV infusion session mimicked the exposure following oral alcohol.

Results: The time course of BrACs following oral alcohol administration showed a high degree of between-subject variability. Mean C_{max}, T_{max}, and AUC did not differ by gender, indicating that calculation of oral doses based on total body water results in comparable BrAC-time courses, on average, for females and males. The IV infusion driven BrAC-time profiles demonstrated good fidelity to the BrAC-time curves resulting from oral alcohol: the mean %difference in C_{max} and AUC were both 11%, while the mean %difference for T_{max} was 27%. This degree of variability is less than half that seen across individuals following oral alcohol administration, which was substantial [coefficient of variation (%CV) ranging from 22 to 52%].

Conclusions: Despite the use of standardized doses and controlled experimental conditions, there was substantial between-subject variability in the BrAC time course following oral administration of alcohol. The PBPK-model-based infusion method can mimic the BrACs attained with oral alcohol for individual subjects. This method provides a platform to evaluate effects attributable to the route of administration on the response to alcohol, as well as the influence of determinants such as family history of alcoholism on the alcohol response.

Key Words: Alcohol Clamp, Route of Administration, Physiologically-Based Pharmacokinetic Model, Pharmacokinetic Variability, Healthy Social Drinkers, Breath Alcohol Concentration.

THE ALCOHOL CLAMP is an alcohol administration method which uses an intravenous (IV) infusion of alcohol to achieve a target breath alcohol concentration (BrAC) at a predetermined time, and then maintain it for a prolonged interval (O'Connor et al., 1998; Ramchandani and O'Connor, 2006; Ramchandani et al., 1999a). This method is based on a physiologically-based pharmacokinetic (PBPK) model for alcohol (Ramchandani et al., 1999a) and provides precise control over the breath and therefore the brain's exposure to alcohol, thus minimizing variation in exposure to alcohol between subjects.

Our previous studies have utilized the alcohol clamp to demonstrate the association of initial and adaptive responses to alcohol with the subjects' family history of alcoholism (FHA). In particular, family history positive (FHP) individuals showed more intense subjective responses than family history negative (FHN) controls on measures of high, intoxication and stimulation during the initial phase of the clamp, and also showed greater acute tolerance to alcohol than FHN individuals on measures of intoxication, as determined during later stages of the clamp after the BrAC was held constant for 105 minutes (Morzorati et al., 2002). FHA-related differences were also observed on saccadic eye-movement measures, with FHP individuals showing longer latencies and slower velocity of random- and antisaccades at baseline, as well as greater tolerance development of antisaccadic latency compared to FHN individuals (Blekher et al., 2002).

Our results, using IV administration of alcohol, differ from those of other studies of FHA influences on the response to alcohol, such as the studies of Schuckit and colleagues (Schuckit, 1984; Schuckit et al., 2000). Among several possible reasons for these differences, the route of alcohol administration was of particular interest because people do not usually infuse alcohol by choice. Thus, it is possible that the route of administration may affect not only the brain's response to alcohol, but also FHA-related differences in those responses.

One approach to examining the hypothesis that the route of administration affects the response to alcohol is to directly compare responses following oral and IV alcohol in the same individuals. There is, however, an approximately 3-fold variance, both between- and within-subjects, in the time course of BrAC achieved following oral alcohol doses, under the best-controlled experimental conditions (Friel et al., 1995). Several sources of pharmacokinetic (PK) variability are controllable, such as the dose per unit body water, rate of ingestion, recent drinking history and food intake. However, many are due to uncontrollable anatomical and physiological factors such as gastric emptying, liver volume and blood flow, which themselves vary as functions of gender, age, ethnicity, family history of alcoholism and genetics (Li et al., 2001; Ramchandani, 2004; Ramchandani et al., 2001). Thus, the impact of the PK variability on the brain's response to alcohol, which can show a 2- to 3-fold variability above and beyond that due to PK, is substantial. Thus, a prerequisite to a comparison of responses following oral and IV alcohol is the development of an IV method that can mimic the time course of BrAC attained with oral alcohol administration in any individual.

Our objectives were to characterize the variability in the time course of breath alcohol concentrations following oral administration of standardized doses of alcohol in healthy volunteers in our laboratory, and to develop an IV infusion method to replicate the BrAC time course attained following oral alcohol in the same subject. Replication would yield comparable breath (and therefore brain) alcohol exposures following oral and IV alcohol administration in the same individual, and permit a direct comparison of any differences in the response to alcohol that are attributable to the route of administration.

METHODS

Study Design

This study was conducted in young adult, healthy, nondependent drinkers. Each subject underwent 2 testing sessions, in the same experimental setting on precisely the same schedule, on different days, separated by a minimum of 3 days. In the first session, subjects ingested an oral dose of alcohol calculated to achieve a peak BrAC of 80 mg%, based on the individual's total body water. In the second session, subjects received an IV infusion of ethanol, administered using a precomputed rate profile designed to achieve the same time course of BrAC as that achieved in the first session. Parameters characterizing each profile were compared to assess how closely the BrAC-time profile from the IV session mimicked the profile from the oral session.

During each session, subjects also undertook a battery of tests, including measures of subjective perceptions, saccadic eye-movements, and resting electroencephalography (EEG). This battery was completed at baseline and serially during both sessions to compare the pharmacodynamics of similar exposures of alcohol administered by 2 different routes of administration. The results for the pharmacodynamic measures will be reported separately.

Subjects

A total of 44 male and female subjects between 21 and 30 years of age (median: 26 years) completed the 2-session study. Subjects were recruited by local advertisement and were screened prior to enrollment into the study. Subjects were nondependent drinkers, as assessed by administration of the alcohol use section of the Semi-Structured Assessment of the Genetics of Alcohol (SSAGA) instrument (Bucholz et al., 1994). FHA status was assessed by the family-history assessment module of the SSAGA instrument. Exclusion criteria were a clinically significant history of renal, hepatic, cardiovascular, pulmonary, or gastro-intestinal disease, any DSM-IIIR Axis I illness including substance dependence (American Psychiatric Association, 1987), history of seizure or loss of consciousness, mental illness requiring hospitalization, or current use of psychoactive medication. Women were studied in the first 14 days following cessation of menses. Smoking was not an exclusion criterion, although subjects were not allowed to smoke once they arrived at the laboratory for the study session. Subjects provided informed consent for the protocol approved by the Institutional Review Board of Indiana University School of Medicine.

Study Session Procedures

Preparation for Testing. Subjects were admitted to the General Clinical Research Center at Indiana University Hospital at 7:30 AM, having been instructed to abstain from alcohol for at least 24 hours and from food for at least 8 hours. All subjects had a zero BrAC measurement on arrival and completed an assessment of recent drinking history using the Timeline Followback (TLFB) computerized questionnaire (Sobell et al., 1988). A negative urine beta-hCG test for pregnancy was obtained from female subjects prior to starting each session. An indwelling catheter was inserted into a vein in the antecubital fossa of each arm, the nondominant arm for the infusion and the dominant arm for blood sampling. At approximately 8:00 AM, subjects ate a 350-calorie breakfast consisting of cereal, milk, toast, and juice. After breakfast, preparation for testing included instruction in the use of the breathalyzer and in the manner in which blood samples for off-line assay of BAC would be obtained.

A practice block of the battery of dependent measures was then administered in order to familiarize the subject with the devices and procedures and to practice the tasks. Following a bathroom break, the baseline measurement of the battery was obtained.

Alcohol Administration. In both sessions, subjects received both an oral drink and an IV infusion, in an attempt to blind the subject to the route by which the alcohol was being administered. During the first session, subjects received the alcohol orally; the required volume of 95% ethanol was calculated from the nomogram published by Watson (1989), and diluted to a final concentration of 20% by volume with diet lemon-lime soda. The nomogram was based on total body water, estimated for each subject using standard equations based on gender, age, height, and weight (Watson et al., 1980). In an attempt to standardize the drinking time to 8 minutes, the total dose was split into 4 equal aliquots and placed in styrofoam cups with lids. The subject was given a cup every 2 minutes with instructions to sip the drink using a straw. At the same time the subjects commenced drinking ($T_{exp} = 0$), an IV infusion of Ringers Lactate was also started, at a constant rate of 30 ml/h.

For the first 3 hours after the start of alcohol administration, serial BrAC measurements were obtained every 2 to 10 minutes using an Alcotest 7410 handheld breath alcohol meter (Drager Safety Inc., Durango, CO). Between study sessions, the recorded time course of BrAC from the first session was approximated by a 10-segment, piecewise-linear function. This function was used as the desired time course of BrAC in the PBPK model for alcohol. The model, which is described more comprehensively in Ramchandani and colleagues (1999a), uses individualized parameters of the subject to compute an infusion rate profile that would replicate the desired BrAC function (Ramchandani et al., 1999a). The resulting infusion rate profile was used in the individual's second laboratory session of the experiment.

During the second session, the subject received the IV infusion rate profile described in the preceding paragraph, using 6% v/v ethanol in Ringers Lactate. The subject also received an oral drink of the same volume as in session 1, divided into 4 aliquots, and administered on the same schedule. However, in an attempt to blind the subject to the route of alcohol administration, each aliquot contained only diet soda with 0.2 ml of 95% ethanol floated on top. The total amount of oral ethanol administered during the second session was only 0.8 g, which was less than 2% of the average session 1 oral dose, and would not be expected to produce any pharmacological effects. At the end of the drinking period in both sessions, subjects rinsed their mouths vigorously with club soda 3 times.

Assessment of the Response to Alcohol. During the ascending, peak, and descending limbs, repeated measurements of subjective, saccadic eye-movement, and EEG responses were obtained, in the same order as in the baseline block. After 3 hours, BrAC measurements were obtained every 15 to 20 minutes until the BrAC fell

below 30 mg%, when subjects were provided with lunch. The subject was discharged when the BrAC fell below 20 mg%. The duration of a typical study session was 8 hours.

Data Analysis

The primary objective of this analysis was to determine the ability of the model-based infusion method to mimic an individual time course of BrAC following oral administration. Three pharmacokinetic parameters that characterize the BrAC vs. time curve were assessed for each session: the peak BrAC (C_{max}), the time of peak BrAC (T_{max}), and the area under the BrAC vs. time curve (AUC). C_{max} and T_{max} were determined by visual observation, and AUC was estimated using the trapezoidal method (for the time interval from the start of alcohol administration until 3 hours later). Additionally, the slope of the regression of the linear portion of the descending limb of the BrAC vs. time curve (DSL, mg%/h) was calculated for each session. The approximate alcohol elimination rate (~AER, g-ethanol/h) in each session was estimated as the product of the individual's DSL and total body water (TBW, L), the latter used as the best estimate of the volume of distribution for alcohol.

For each subject, the %absolute difference (delta%Abs) for each PK parameter between the 2 sessions (|IV–Oral|/Oral) was computed to evaluate the magnitude of the difference in the BrAC exposure between the sessions.

Statistical Analysis

Demographic characteristics were compared between males and females using unpaired *t*-tests. The PK parameters (C_{max}, T_{max}, AUC, DSL, and AER) following oral alcohol administration were compared between males and females using unpaired *t*-tests. Descriptive statistics for the %difference for each parameter as well as the engineering metric were tabulated. The PK parameters were compared between the oral and IV sessions using repeated measures ANOVA. The α level for significance was set at 0.05. Statistical analyses were performed using Statview (version 5.0.1, SAS Institute Inc., Cary, NC).

RESULTS

Subject Demographics

Forty-four subjects (22 females and 22 males) completed both sessions of the study. Table 1 shows the characteristics of the 44 subjects. Expected significant gender differences in height, weight, and total body water were observed. All subjects tolerated all sessions well, with no incidence of nausea or any other untoward effect. The most common reported

Table 1. Subject Characteristics

	Females (n = 22)	Males (n = 22)	p-value for gender difference
Age (years; mean ± SE)	26 ± 0.4	25 ± 0.6	0.2678
Height (cm; mean ± SE)	166.9 ± 1.4	182.9 ± 1.9	<0.0001
Weight [kg; mean ± SE (range)]	71.0 ± 2.4 (52.9–95.0)	86.7 ± 4.0 (55.7–133.0)	0.0020
Total body water[a] [l; mean ± SE (range)]	33.3 ± 0.6 (28.1–38.8)	48.9 ± 1.5 (37.5–63.9)	0.0001
Number of smokers	4	4	–
Recent drinking history			
Number of drinks in 28-day interval	19	26	0.2764
Number of drinking occasions in 28-day interval	7	8	0.8060

[a]TBW estimated using standard equations for males and females based on age, height, and weight (Watson et al., 1980).

side-effect was headache, which generally occurred at the end of the experimental session.

Pharmacokinetics of Oral Alcohol: Gender Differences

Figure 1*A* and *B* shows the observed BrAC vs. time profiles for the male and female subjects in the study, and illustrates the substantial variability in systemic alcohol concentrations following oral administration. The mean observed peak BrAC (C_{max}) was 81 mg%, almost exactly at the target level (80 mg%). The C_{max}, however, showed a 2.5-fold range (49 to 126 mg%) across subjects. The time of occurrence of the peak BrAC (T_{max}) also showed substantial variation across subjects, ranging from 15 minutes to 127 minutes following the start of alcohol administration (an 8-fold range). The AUC showed a 3-fold range across subjects.

Table 2 lists the mean ($\pm$ SE) PK parameters, by gender, for the oral alcohol session. Mean peak BrAC (C_{max}), time of peak BrAC (T_{max}), and AUC did not differ by gender, documenting that calculation of oral doses based on total body

Table 2. Pharmacokinetic Parameters for Alcohol Following Oral Administration, by Gender

|	Females ($n = 22$) Mean ± SE (%CV)	Males ($n = 22$) Mean ± SE (%CV)	p-value for gender difference
Dose			
g	34.1 ± 0.7 (10)	49.5 ± 1.4 (13)	–
g/kg body weight	0.49 ± 0.01 (8)	0.58 ± 0.01 (9)	–
C_{max} (mg%)	79.0 ± 3.4 (20)	86.0 ± 4.3 (24)	0.2017
T_{max} (minutes)	49 ± 5 (48)	52 ± 6.3 (57)	0.7413
AUC (mg%·h)	8,929 ± 367 (19)	10,016 ± 441 (21)	0.0651
DSL (mg%/h)	16.8 ± 0.6 (16)	15.2 ± 1.0 (30)	0.1556
~AER (g/h)	5.6 ± 0.2 (19)	7.4 ± 0.5 (32)	0.0021

%CV, coefficient of variation.

water results in comparable BrAC-time courses, on average, for females and males. The estimates of DSL and AER are consistent with values previously reported in the literature for alcohol (Ammon et al., 1996; Kwo et al., 1998; Thomasson et al., 1995). There was no statistically significant difference in
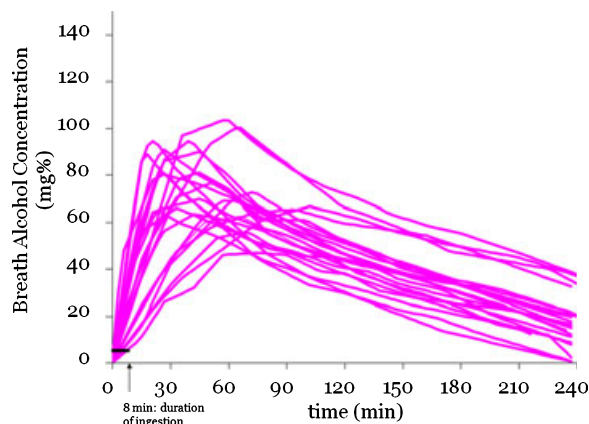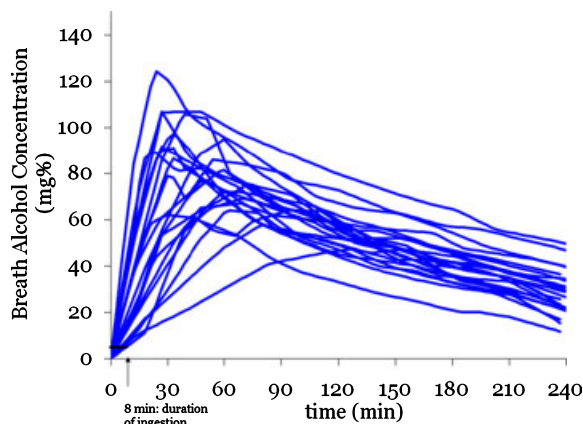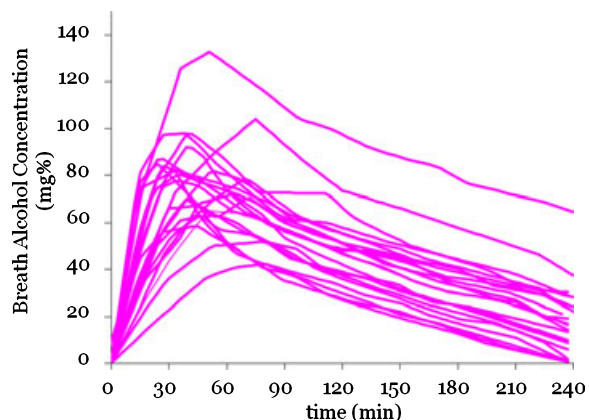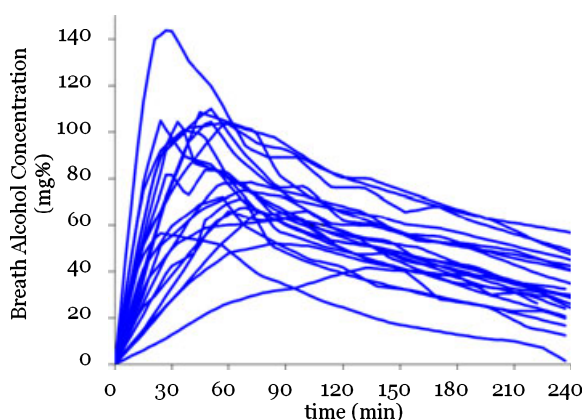

Fig. 1. Breath alcohol concentration versus time profiles following oral administration (1 g/l total body water) for female subjects (Panel **A**, $n = 22$) and male subjects (Panel **B**, $n = 22$), and following IV ethanol administration for female subjects (Panel **C**, $n = 22$) and male subjects (Panel **D**, $n = 22$).

the descending limb slope between males and females, however there was a significant difference in ~AER by gender ($p = 0.0021$). This is probably a result of the significant differences in TBW between males and females in the study. Also, the estimate of ~AER obtained as the product of DSL and TBW is only an approximation to the best estimate of alcohol elimination rate, obtained from the steady-state infusion rate during a clamp (Kwo et al., 1998; O'Connor et al., 1998).

Pharmacokinetics of IV Alcohol: Comparison With Oral Administration

Figure 1C and D shows the observed BrAC vs. time profiles following IV alcohol administration in the male and female subjects in the study. Figure 2A shows the time course of BrAC for 2 subjects for the oral and IV sessions, and illustrates the ability of the model-based IV infusion to mimic the BrAC-time course obtained following oral alcohol administration. The subjects depicted in Fig. 2A reflect the most

Panel A

Panel B

Fig. 2. (**A**) Mimicking the BrAC-time profile following oral alcohol administration (open symbols) using the PBPK-model-based infusions (closed symbols) for 2 typical subjects, a010, a 73 kg male (circles) and a069, a 63 kg female (triangles). (**B**) Time course of mean (solid line) ± SD (broken lines) of individual difference in BrACs between oral and IV sessions.
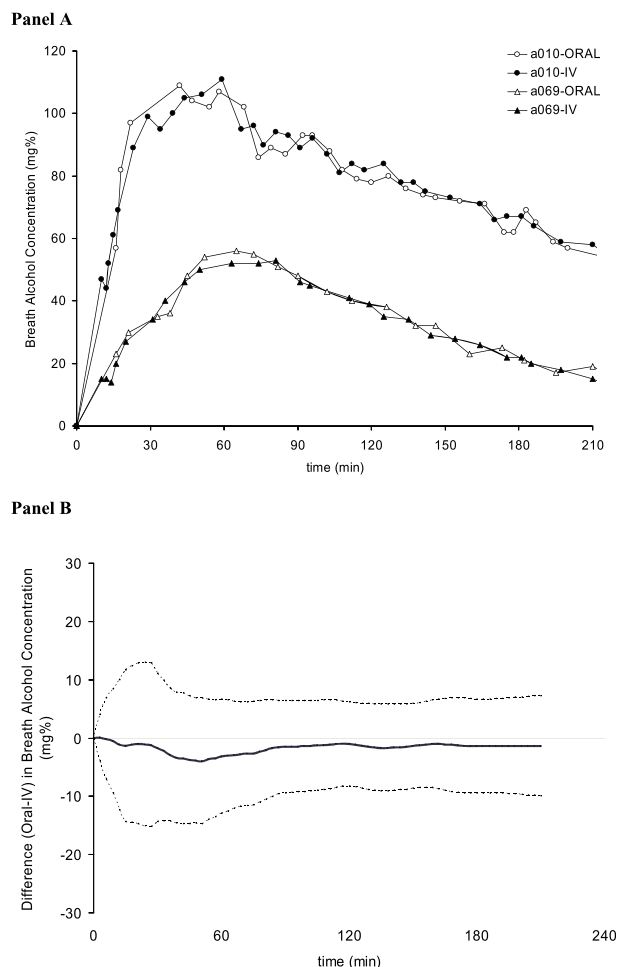
extreme cases with respect to BrAC exposure and were selected to emphasize the large inter-individual differences in BrAC-time curves following identical standardized doses. The result for the overall sample is that the difference between the time courses of BrACs in oral and IV sessions for any individual is small, as characterized for the entire sample in Fig. 2B. As expected, the between-subject variation of all 44 subjects in the study following IV alcohol administration is the same as that following oral administration. Table 3 lists the pharmacokinetic parameters for alcohol following oral and IV administration in separate sessions. Due to the lack of gender differences seen in previous analyses, the parameters were compared between the sessions for all subjects. There were no significant differences observed between the PK parameters obtained from the oral and IV session data.

Table 3 also shows the mean % absolute differences (delta%Abs) between the parameters obtained in the 2 sessions. The mean delta%Abs for C_{max} was 11% (corresponding to a difference in BrAC of about 10 mg%), and ranged from 0 to 30% across subjects. Similarly, the mean delta%Abs for T_{max} was 11% (corresponding to a difference of 12 minutes), but ranged from 0 to 119% across subjects. There was a large range in values for the delta%Abs across parameters within an individual, although the variation was approximately half the variability seen in the parameters between individuals, with coefficients of variation (%CVs) ranging from 19 to 52% across parameters and sessions.

DISCUSSION

The first objective of this study was to characterize the variability in BrAC exposure following standardized oral alcohol administration in male and female social drinkers. Results revealed a high degree of variability in peak BrAC, time of peak BrAC as well as the AUC following oral alcohol administration in young healthy social drinkers (%CV ranging from 22 to 52%). This was observed despite controlling several of the known sources of variance in alcohol absorption and metabolism, such as time of day, food intake, type, and concentration of the beverage and duration of drinking, as well as compensating for variation due to individual factors such as gender, height, weight, and age by adjusting the dose of ethanol based on total body water to account for differences in volume of distribution of alcohol. While these procedures resulted in average peak BrACs and time to peak BrACs that were not significantly different from each other, by gender, substantial inter-individual variability remained in both groups. There was also substantial inter-individual variability in the measures of alcohol metabolic rates (DSL and ~AER), however a gender difference was not seen in the descending limb slope (DSL), as has been previously reported (Thomasson, 2000; Thomasson et al., 1995).

The second objective of this study was to examine the ability to replicate or mimic the oral BrAC vs. time curve (obtained following oral alcohol administration) using a PBPK-model-based IV infusion method. Results revealed

Table 3. Pharmacokinetic Parameters for Alcohol Following Oral and IV Administration (n = 44)

	Oral session Mean ± SE (%CV)	IV session Mean ± SE (%CV)	Delta%Abs |IV − Oral|/Oral (%) Mean	Range
C_{max} (mg%)	82.5 ± 2.8 (22)	84.6 ± 3.5 (28)	11	0–30
T_{max} (minutes)	51 ± 4 (52)	51 ± 3 (44)	27	0–119
AUC (mg%·h)	9,473 ± 296 (21)	9,756 ± 423 (29)	11	0–39
DSL (mg%/h)	16.0 ± 0.6 (24)	16.0 ± 0.5 (19)	11	0–35
∼AER (g/h)	6.5 ± 0.3 (31)	6.5 ± 0.2 (25)	11	0–35

high fidelity of the BrAC curve following IV infusion to that obtained following oral alcohol: the mean %difference in C_{max} and AUC were both 11%, while the mean %difference for T_{max} was 27%. This degree of variability is less than half the variability seen between individuals following oral alcohol administration, which was substantial (%CV ranging from 19 to 52%). The large inter-individual variability seen following oral alcohol was also replicated in the measures obtained following IV alcohol. Thus, the infusion method allowed replication of the time course of each individual's brain exposure to alcohol, and consequently replicated the inter-individual variability seen following oral alcohol. The ability to mimic the oral data IV infusion permits a direct comparison of differences in the pharmacodynamic responses attributable to route of administration. One constraint that ensues from the inability to predict the individual's time course of BrAC following oral administration, however, is that the experiment we conducted required a fixed order of route of administration between sessions.

The results of this study are consistent with the studies by Friel and colleagues (1995, 1999), which aimed to characterize the inter-subject variability in BrACs in an oral alcohol challenge study in a large group of male and female subjects. Despite efforts to control the experimental conditions and standardize the ethanol dose based on total body water, they obtained peak BrACs that ranged from 33 to 126 mg% across subjects, and showed significant gender differences. Tmax ranged from 10 to 91 minutes from the start of drinking (Friel et al., 1995), which is similar to the range of BrACs observed in our study. In a follow-up study, Friel and colleagues (1999) adjusted their dosing guidelines to reduce the ratio of doses administered to males and females in order to obtain equivalent peak BrAC levels, and standardized the duration of drinking. The results of their second study showed that peak BrAC levels were not significantly different between male and female subjects, however there was still substantial variability (about 2-fold) in BrACs between individuals. Another study, in which oral alcohol doses were computed for healthy male and female subjects based on total body water, showed no significant differences between average peak BrACs in men and women, but did show a large variability in BrACs with %CVs of about 25% (Breslin et al., 1997). Our results agree with those from the above-mentioned studies: in a group, desired average peak BrACs can be achieved, but there is very little that can be done to control the individual variation in pharmacokinetics and the time course of brain exposure to alcohol following oral administration of alcohol. The between-subject variability in alcohol pharmacokinetics must be taken into account when analyzing the pharmacological effects of alcohol on the brain and other organs, although this is not done frequently.

One method for reducing variability in systemic (including brain) exposure to alcohol would be to avoid the chief source of variability, i.e., the oral route of administration. Instead, the alcohol can be infused intravenously using a rate profile that achieves the same desired time course of BrAC (Ramchandani et al., 1999a) in every subject. The foundation of this approach is a PBPK-model for alcohol. The model parameters are individualized for each subject and used to compute the infusion profile to achieve a desired time course of BrAC exposure, that is precise and reliably obtained (± 5 mg%) in each individual. Our previous work has used the model-based method to obtain a steady-state BrAC exposure (called the alcohol clamp), and examine various aspects of the pharmacokinetics and pharmacodynamics of alcohol (Blekher et al., 2002; Gilman et al., 2008; Kwo et al., 1998; Morzorati et al., 2002; Neumark et al., 2004; O'Connor et al., 1998, 2000; Ramchandani et al., 1999b, 2002, 2006). Thus, the use of IV alcohol, combined with a model-based approach, allows precise, accurate, and reliable control of the exposure *across* individuals, and is, we believe, the method of choice if *every* subject in a study needs to be exposed to the *same* time course of BrAC.

As with all methods, there are some limitations and considerations with the use of IV administration methods in alcohol challenge studies. The IV method does require the insertion of an IV catheter into an arm vein by a trained nurse or physician, which is a routine and safe procedure, although there is an uncommon but real risk of bruising, local pain, irritation, and infection associated with the actual IV catheterization and infusion. The IV method also necessitates the use of a precise and accurate infusion pump, which can cause some limitation in movement of subjects connected to an infusion pump, although mobility can be improved by attaching the pump to a IV pole on wheels. Finally, as discussed previously, concerns have been raised about the generalizability of results obtained from IV alcohol studies to other studies using the more naturalistic oral alcohol administration methods. This was, in fact, the rationale for undertaking this comparison study, and the results of analyses comparing the brain's response to alcohol administered by the oral and IV routes will be published separately.

In summary, we have demonstrated that the ability to replicate the time course of BrAC following oral alcohol administration using an IV infusion. The PBPK-model-based infusion method could also be used to control the rate of change (or slope) of BrAC as a function of time, and we are engaged in studies to examine if the rate of change of BrAC has a direct effect on the brain's response to alcohol. If so, then the unavoidable PK variability following oral administration of alcohol would need to be accounted for in analyses of the effects of determinants of the pharmacodynamic responses.

REFERENCES

Ammon E, Schäfer C, Hofmann U, Klotz U (1996) Disposition and first-pass metabolism of ethanol in humans: is it gastric or hepatic and does it depend on gender? Clin Pharmacol Ther 59:503–513.

Blekher T, Ramchandani VA, Flury L, Foroud T, Kareken D, Yee RD, Li T-K, O'Connor S (2002) Saccadic eye movements are associated with a family history of alcoholism at baseline and after exposure to alcohol. Alcohol Clin Exp Res 26:1568–1573.

Breslin FC, Kapur BM, Sobell MB, Cappell H (1997) Gender and alcohol dosing: a procedure for producing comparable breath alcohol curves for men and women. Alcohol Clin Exp Res 21:928–930.

Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JIJ, Reich T, Schmidt I, Schuckit MA (1994) A new semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. J Stud Alcohol 55:149–158.

Friel PN, Baer JS, Logan BK (1995) Variability of ethanol absorption and breath concentrations during a large-scale alcohol administration study. Alcohol Clin Exp Res 19:1055–1060.

Friel PN, Logan BK, O'Malley D, Baer JS (1999) Development of dosing guidelines for reaching selected target breath alcohol concentrations. J Stud Alcohol 60:555–565.

Gilman JM, Ramchandani VA, Davis MB, Bjork JM, Hommer DW (2008) Why we like to drink: a functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. J Neurosci 28:4583–4591.

Kwo PY, Ramchandani VA, O'Connor S, Amann D, Carr LG, Sandrasegaran K, Kopecky KK, Li TK (1998) Gender differences in alcohol metabolism: relationship to liver volume and effect of adjusting for body mass. Gastroenterology 115:1552–1557.

Li TK, Yin SJ, Crabb DW, O'Connor S, Ramchandani VA (2001) Genetic and environmental influences on alcohol metabolism in humans. Alcohol Clin Exp Res 25:136–144.

Morzorati SL, Ramchandani VA, Flury L, Li T-K, O'Connor S (2002) Self-reported subjective perception of intoxication reflects family history of alco-

holism when breath alcohol levels are constant. Alcohol Clin Exp Res 26:1299–1306.

Neumark YD, Friedlander Y, Durst R, Leitersdorf E, Jaffe D, Ramchandani VA, O'Connor S, Carr LG, Li T-K (2004) Alcohol dehydrogenase polymorphisms influence alcohol-elimination rates in a male Jewish population. Alcohol Clin Exp Res 28:10–14.

O'Connor S, Morzorati S, Christian J, Li T-K (1998) Clamping breath alcohol concentration reduces experimental variance: application to the study of acute tolerance to alcohol and alcohol elimination rate. Alcohol Clin Exp Res 22:202–210.

O'Connor S, Ramchandani VA, Li T-K (2000) PBPK modeling as a basis for achieving a steady BrAC of 60 ± 5 mg% within ten minutes. Alcohol Clin Exp Res 24:426–427.

Ramchandani VA (2004) Genetic aspects of alcohol metabolism, in Nutrition and Alcohol: Linking Nutrient Interactions and Dietary Intake (Watson RR, Preedy VP eds), pp 187–199. CRC Press, Boca Raton.

Ramchandani VA, Bolane J, Li T-K, O'Connor S (1999a) A physiologically-based pharmacokinetic (PBPK) model for alcohol facilitates rapid BrAC clamping. Alcohol Clin Exp Res 23:617–623.

Ramchandani VA, Bosron WF, Li TK (2001) Research advances in ethanol metabolism. Pathol Biol (Paris) 49:676–682.

Ramchandani VA, Flury L, Morzorati SL, Kareken D, Blekher T, Foroud T, Li T-K, O'Connor S (2002) Recent drinking history: association with family history of alcoholism and the acute response to alcohol during a 60 mg% clamp. J Stud Alcohol 63:734–744.

Ramchandani VA, O'Connor S (2006) Studying alcohol elimination using the alcohol clamp method. Alcohol Res Health 29:286–290.

Ramchandani VA, O'Connor S, Blekher T, Kareken D, Morzorati S, Nurnberger J Jr, Li T-K (1999b) A preliminary study of acute responses to clamped alcohol concentration and family history of alcoholism. Alcohol Clin Exp Res 23:1320–1330.

Ramchandani VA, O'Connor S, Neumark Y, Zimmermann US, Morzorati SL, de Wit H (2006) The alcohol clamp: applications, challenges, and new directions–an RSA 2004 symposium summary. Alcohol Clin Exp Res 30:155–164.

Schuckit MA (1984) Subjective responses to alcohol in sons of alcoholics and control subjects. Arch Gen Psychiatry 41:879–884.

Schuckit MA, Smith TL, Kalmijn J, Tsuang J, Hesselbrock V, Bucholz K (2000) Response to alcohol in daughters of alcoholics: a pilot study and a comparison with sons of alcoholics. Alcohol Alcohol 35:242–248.

Sobell LC, Sobell MB, Leo GI, Cancilla A (1988) Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. Br J Addictions 83:393–402.

Thomasson HR (2000) Alcohol elimination: faster in women? Alcohol Clin Exp Res 24:419–420.

Thomasson HR, Beard JD, Li T-K (1995) ADH2 gene polymorphisms are determinants of alcohol pharmacokinetics. Alcohol Clin Exp Res 19:1494–1499.

Watson PE (1989) Total body water and blood alcohol levels: updating the fundamentals, in Human Metabolism of Alcohol, Vol. 1 (Crow KE, Batt RD eds), pp 53–54. CRC Press, Boca Raton.

Watson PE, Watson ID, Batt RD (1980) Total body water volumes for adult males and females estimated from simple anthropometric measurements. Am J Clin Nutr 33:27–39.